HAZARD IDENTIFICATION OF METALWORKING FLUIDS

'Nieuwe kijk op een greswaarde voor metaalbwerkingsvloeistoffen'
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HAZARD IDENTIFICATION OF MINERAL OILS

HAZARD IDENTIFICATION: MINERAL OILS

General Characteristics of mineral oils:

- Petroleum derived substances obtained through vacuum distillation
  - Paraffinic or naphthenic (Carbon range; C12-120)
- Complex Substances (not mixtures!),
  - UVCBs (Unknown or Variable Composition, Complex reaction products or Biological Materials)
- Defined Physicochemical properties
  - Range of physicochemical values (not fixed point values!)
    - Boiling point: 200-800°C
    - Flash point: 98-344°C
    - Vapour pressure: <0.1 hPa (at 20°C)
    - Viscosity: 2-847 mm^2/s (at 40°C)
- No Flammability hazard; but potential Aspiration Hazard.

HAZARD IDENTIFICATION: MINERAL OILS

General Characteristics of mineral oils:

- Physicochemical properties → linked to toxicological properties
- Highly irritating components are boiled out
  - C9-C16 alkanes (kerosene, BP: 90~280°C)
- Low Boiling point aromatics not present (e.g. Toluene, Benzene)
- Some high boiling point aromatics are toxic
  - PAC, PAH
- Treatment of mineral oils renders a less toxic material
  - Hydrotreatment,
  - Solvent Extraction

TOXICOLOGY DATA: MINERAL OILS - TOXICOKINETICS

Toxicokinetics (ADME)

- Adsorption
  - Indirectly proportional to Carbon chain length
    - C14 → 60% ; C28 → 5%
  - Oral dose, 98% excreted unchanged, ~2% absorbed in the intestine
- Distribution
  - Blood → trace levels (< 0.01%)
  - Heart (0.08%), kidney (1.4%), mesenteric lymph node (0.2%); also in liver and brain
  - C-range in heart and kidney → C14-34 ; peak C24-26
  - C-range in small intestine and faeces → C14-38 ; peak C21-22

TOXICOLOGY DATA: MINERAL OILS - TOXICOKINETICS

Toxicokinetics (ADME)

- Metabolism
  - High carbon chain length are not metabolized
  - Shorter chains, C16-C18 → respective fatty acids
- Excretion
  - 98% excreted via faeces
  - Accumulation of oil in liver, mesenteric LN, and fat
    - depends on oil viscosity
    - SD rat accumulates 50% less than F-344 in liver. Little difference in MLN

TOXICOLOGY DATA: MINERAL OILS – ACUTE TOXICITY

Acute toxicity

- Oral LD50 > 5000 mg/kg (high and low refinement)
- Dermal LD50 >5000 mg/kg (high); >2000 mg/kg (low refinement)
- Inhalation LC50 (4h) > 5.5 mg/L (high refinement)

Accidental ingestion of mineral oil may lead to aspiration hazard if vomiting is provoked.

Aspiration hazard is related to viscosity and surface tension.

Local Effects

- Irritation: Not irritant for skin, eyes. For inhalation except for high aerosols concentrations.
- Sensitisation: Skin and Inhalation not sensitising (no hapten formation)

Repeated dermal exposure to oils may lead to skin defatting and cracking.

TOXICOLOGY DATA: MINERAL OILS – CHRONIC TOXICITY

Chronic toxicity

- Repeated dose toxicity (90-days; sub-chronic)
  - Oral: no data →worse case read across DAE, LOAEL =125 mg/kg bw
  - Dermal: NOAEL = 2000 mg/kg bw (high ref.) ; NOAEL = 30 mg/kg bw (low ref.)
  - Inhalation: NOAEL = 50- 500 mg/m^3 (high ref.)
- Critical effects (Pathology)
  - Oral route: Liver granulomas, and Mesenteric lymph node histocytosis is specific for F-344 rats. These effects are not relevant to humans.
  - Oral an Dermal routes: Low refinement oils show similar effects in bone marrow, adrenals, liver, spleen
  - Inhalation route: oil deposition, macrophage accumulation in alveoli, inflammation

TOXICOLOGY DATA: MINERAL OILS – CHRONIC TOXICITY

Chronic inhalation (aerosols and mist)

Severity of macorphage accumulation in alveoli

- For mineral oils, severity of macrophage accumulation in alveoli follows a dose-response
  - Low, 50 – 5 00 mg/m3 (occasional) [NOAEL]
  - 4 fold over low level, 1000-1500 mg/m3 (thickened alveolar wall)
- For formulated oils (~2% additive) the dose response is less uniform, depending on the formulated oil
  - No clear NOAEL
  - NOAEL may be lower than mineral oil depending on formulation

Walden et al. 2003. Respiratort Toxicology of Mineral Oils. Appl. Occp. Environ. Hyg 18, 921-929

TOXICOLOGY DATA: MINERAL OILS – CHRONIC TOXICITY

Mutagenicity

- In vitro
  - Negative for high refinement
  - Positive for low refinement
- In vivo
  - Negative for low and high refinement

ARE MINERAL OILS CARCINOGENIC?

Carcinogenicity

- By far the most relevant critical effect
- Depends on refinement history
- Mineral oils contain aromatic components
  - *Aromatics*:
    - Single or multiple ring systems
    - Virtually all are alkylated (different degree)
    - Multiple ring systems: PAH or PAC
  - 3-7 ring (specially 4-6) PAC have been shown to cause tumors in humans and animals
- Need to distinguish those oils which are carcinogenic
  - Need to refine oils to decrease the amounts of PAC
  - Need to assess the relationship between PAC and cancer
  - Relationship PAC/cancer does allow predicting the hazard

CARCINOGENICITY DETERMINATION OF MINERAL OILS

- Carcinogenicity of oils → simultaneous presence of all PAC
- NOT possible to determine hazard by single components

Health hazard: By large, biggest concern is **skin** cancer

Carcinogenic potential: skin painting studies

- Mice, 2 year long
- Test item is applied to the shorn back of mice
- Endpoint: formation of tumors (benign / malignant)
- **Observation: Carcinogenicity of oils is a function of PAC content *at tissue level* and not of dose *volume* on the skin area. (Roy et al. 1988)**
- No dose response possible → no DNEL
- Carcinogenicity testing becomes pass/fail testing

CARCINOGENICITY DETERMINATION OF MINERAL OILS

Refinery batches must be regularly checked for health hazard

- Routine 2-year skin painting studies not possible
- Other reliable routine tests must be available.

Oil Industry Standards based on DMSO extraction:

- IP 346
- Modified Ames Test

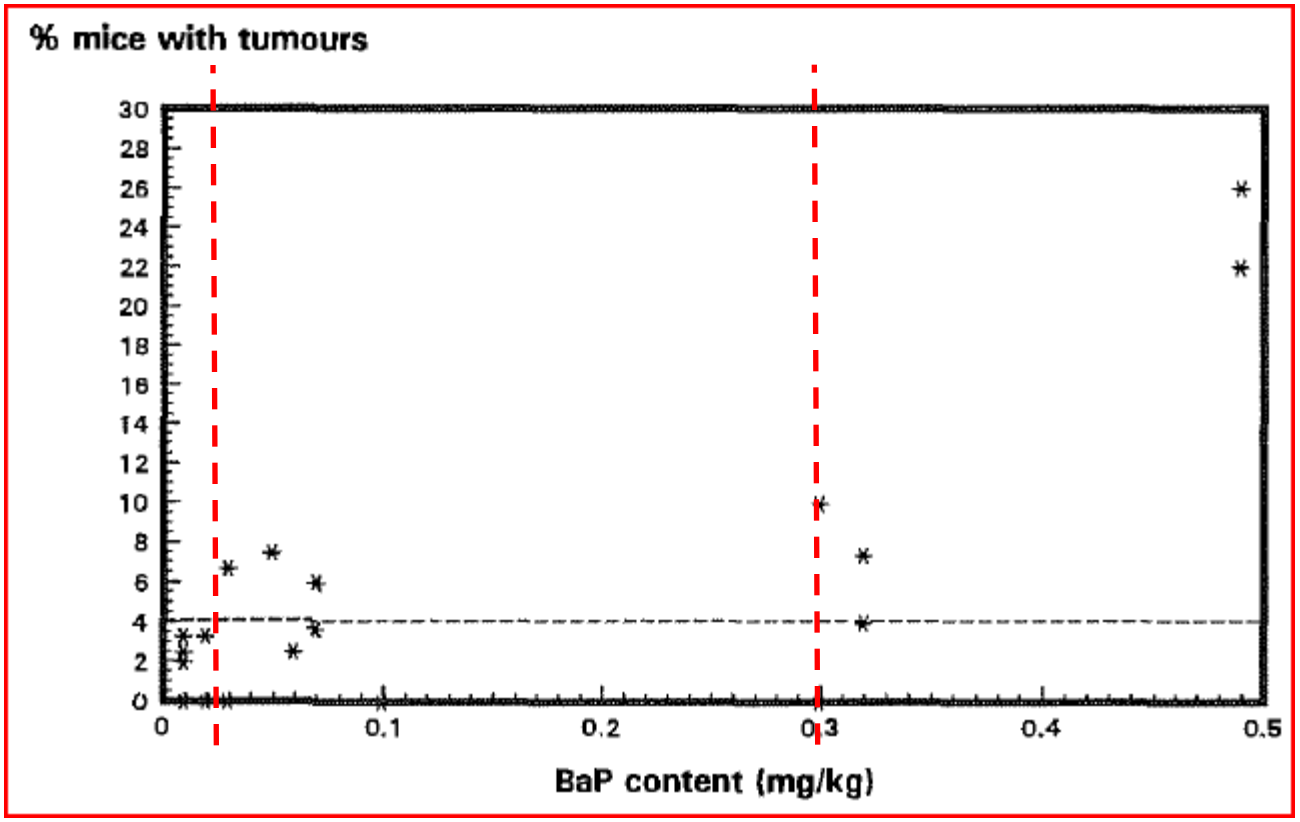
IP 346: METHODOLOGY

- Reliable, routine testing method for carcinogenicity of mineral oils
- Replaces the murine skin painting study
- Gravimetric method (mass %)
- Oil sample is extracted twice with DMSO
- Extracted materials are 3-7 PAC but other material is also extracted
- IP 346 < 3% (no R45), IP 346 $\geq$ 3% (cat 2. R45)
- Adopted in the EU for classification and labeling

IP 346: CARCINOGENICITY PREDICTION

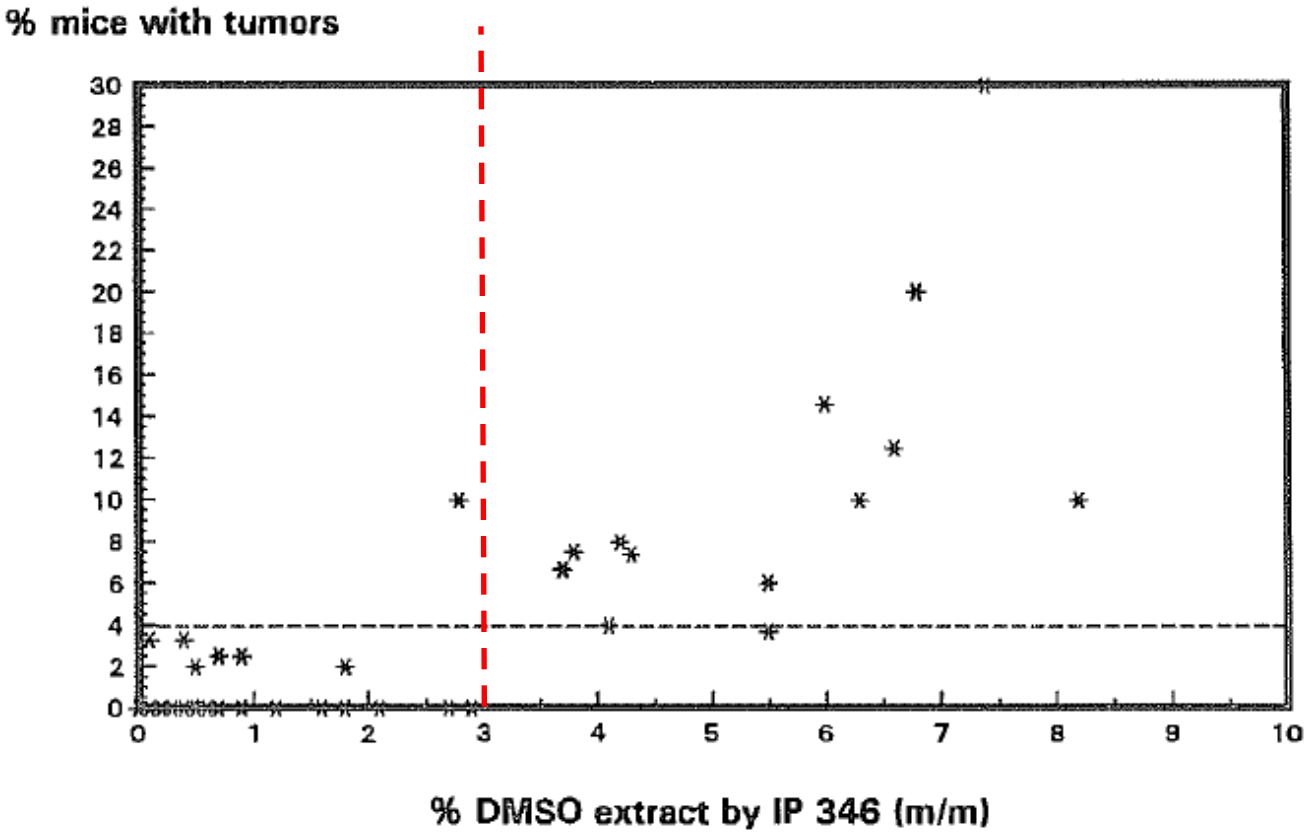
- Skin painting studies: Conservatively, 4% of mice with tumors → significant
- 4% mice with tumors → cut-off in tested oils for carcinogenic vs. non-carcinogenic
- Data pool ~ 76 skin painting studies
- Two discriminators: Benzo[a]pyrene or DMSO extract by IP 346?

IP 346: DISCRIMINATOR, BENZO[a]PYRENE



- Hazard determination by single components is not adequate!
- Benzo[a]pyrene alone as a marker in oils not accurate to discriminate

IP 346: DISCRIMINATOR, DMSO EXTRACT



- Hazard determination should always be on the whole stream!
- DMSO extract by IP 346 → one false negative

IP 346: ACCURACY OF THE TEST

Prediction	DMSO extract marker level (% m/m)		
	1%	2%	3%
Correct positive predictions	37	36	34
Correct negative predictions,	51	57	64
False positive predictions	16	10	3
False negative predictions	0	1	3

- Updated performance of the IP-346 (1994)
- 2 false negatives were at 5% tumor incidence, close to the 4% tumor incidence cut off level. 1 false negative was at 10% tumor incidence.

IP 346: CONFIRMATORY STUDIES

Is 3% IP346 justified?

Dilution blends:

- Samples which tested positive
- 3 diluted samples with white oil (blend) for a final formulation of IP 346< 3% (2) and >3% (1)
- Samples < 3% IP346 (-); and sample > 3% (+)
- Blends of neg. samples with IP346< 3%, again negative.

MODIFIED AMES TEST

DMSO extraction of a mineral oil applied to an Ames Test in a modified version

- Modifications from standard Ames test:
  - 8x higher levels of S9 (Hamster, not rat) fraction
  - 2x higher cofactor NADP
- Modified Ames' performance (n=57; tested oils)

	≤ 4% mice with tumors	>4% mice with tumors
MI ≤1	28	0
MI >1	0	29

OILS IN THE MARKET

In 2003 *Mackerer et al.* reported current oil Hazard specs in the US market (n=53)

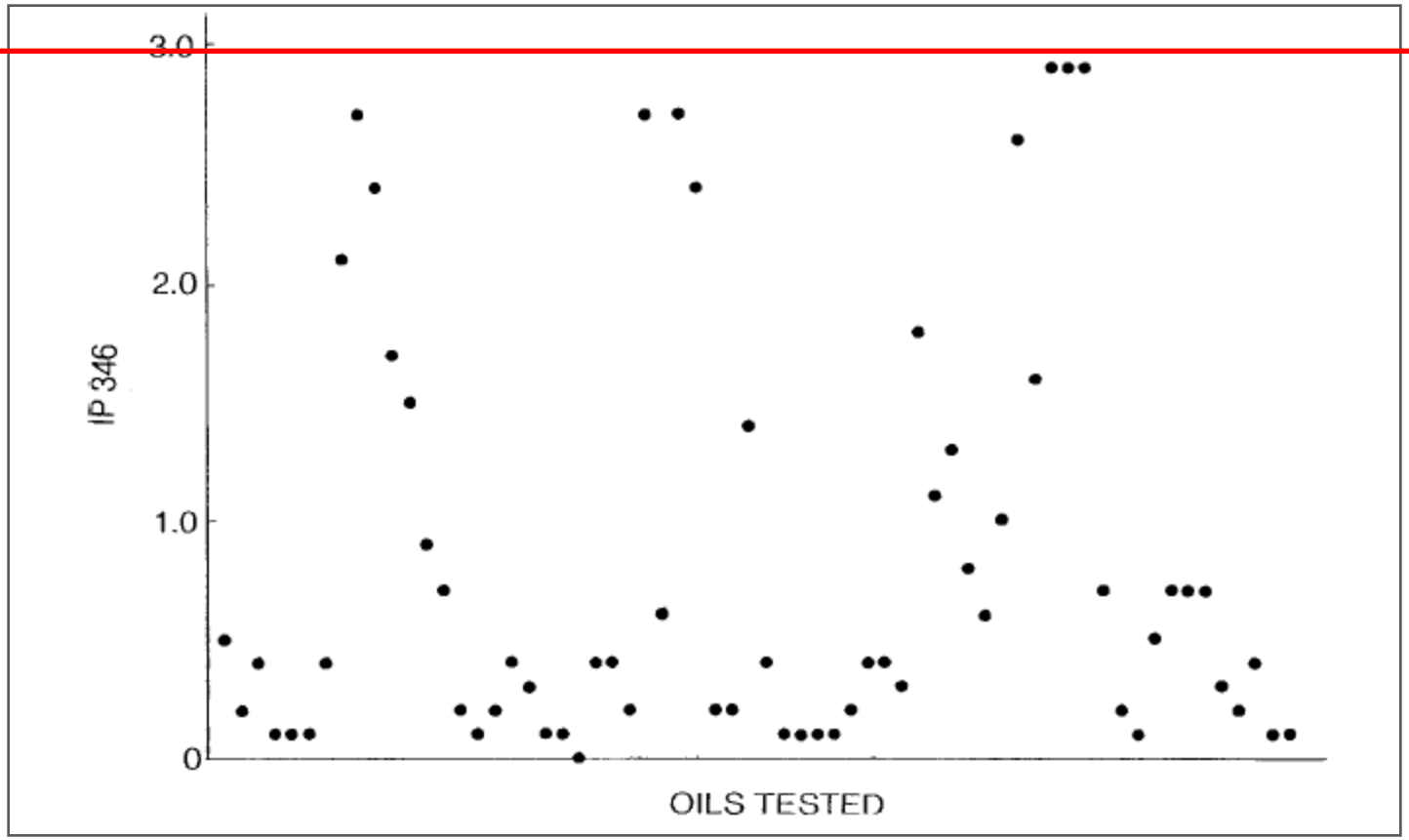
All samples collected tested for

- Mod. Ames test
- IP 346

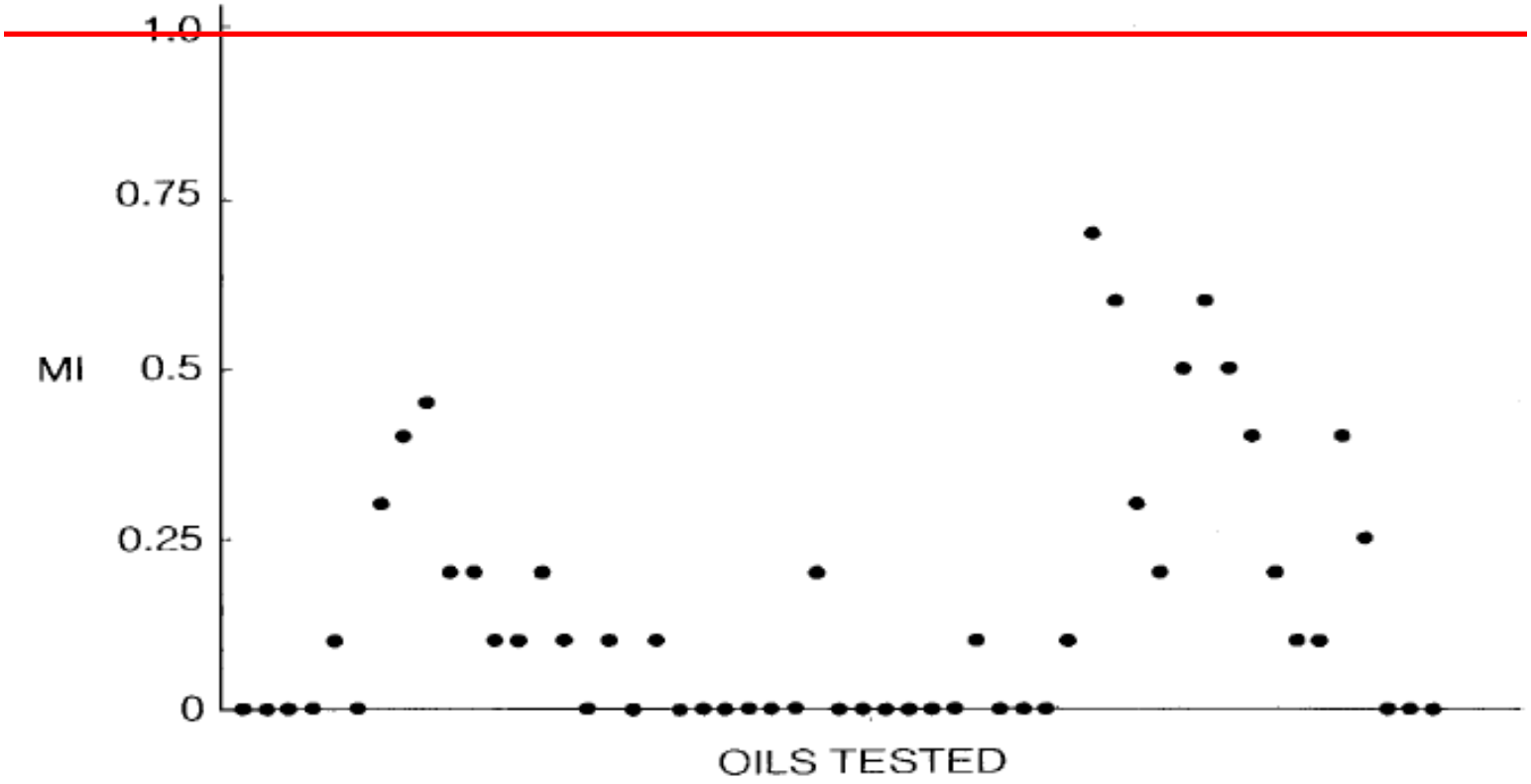
All samples were <3% IP346 and MI <1.

C. Mackerer; et al. 2003. **Petroleum Mineral Oils Refining and Evaluation of Cancer Hazard**. Appl. Occup. Envi. Hygiene, 18: 890-901

OILS IN THE MARKET, IP 346



OILS IN THE MARKET, MI



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SUMMARY: HAZARD IDENTIFICATION OF MINERAL OILS

SUMMARY: TOXICOLOGICAL HAZARDS OF MINERAL OILS

- Complex UVCB substances
- Toxicological properties are defined by physical chemical properties
- Acute toxicity and irritancy is low
- Chronic toxicity is driven by PACs
- Lowering PAC content (solvent extraction and hydro treatment) → lower health hazard
- By far carcinogenicity is the most relevant critical effect
- Assessing carcinogenicity of UVCBs by single PACs is difficult
- Carcinogenicity of refined oils is predicted by IP 346 method
- IP 346 is based on the whole substance and not on single components
- Oils with IP346< 3% are not considered carcinogenic

SUMMARY: TOXICOLOGICAL HAZARDS OF MINERAL OILS

- Threshold effects of mineral oils allow a derivation of a DNEL
- Worker, Local effects, long term exposure (8h)
- Based on respiratory effects; inflammation, hyperplasia and squamous metaplasia (benign changes in epithelium) of the nasal mucosa

	effect	route	DNEL	dose descriptor	Mod dose and AF
Acute	systemic	all	-		
	local	all	-		
Chronic	systemic	dermal	-		
		inhalation	-		
	local	dermal			
		inhalation	**5.4 mg/m3/8h [aerosol]**	500 mg/m3 [NOAEC]	251 mg/m3/8h ; AF=45

Q & A